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**Official Title:**

A Prospective, Randomized Trial Evaluating Regional Anesthesia, Long-Acting Local Anesthesia, and Traditional Care for Pain Control of Operatively Treated Ankle Fractures

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## 1. Title

A Prospective, Randomized Trial Evaluating Regional Anesthesia, Long-Acting Local Anesthesia, and Traditional Care for Pain Control of Operatively Treated Ankle Fractures

## 2. External IRB Review History

N/A

## 3. Prior Approvals

N/A

## 4. Objectives

This study is a multicenter, three armed, prospective randomized control trial studying the effect of a long-acting local anesthetic “cocktail” in patients undergoing operative fixation of ankle fractures.

### Primary Hypothesis Driven Aims:

1. **Determine the effectiveness of a local anesthesia “cocktail” compared to regional block or standard of care in controlling pain in operatively treated ankle fractures.** Nearly one out of ten fractures treated by both orthopaedic traumatologists and general orthopaedic surgeons taking call are ankle fractures. As such, effective pain control in this group of patients represents an opportunity to make a large impact, especially in the context of the current opioid epidemic. Improved pain control can help improve patient satisfaction, outcomes, decrease length of stay, cost of care, and complications associated with traditional narcotic use.
  - **Hypothesis 1A:** Patients receiving the intraoperative cocktail will have improved post-operative pain control compared to those receiving a peri-operative nerve block or standard of care.
  - **Hypothesis 1B:** Patients receiving the intraoperative cocktail or peri-operative nerve block will have improved post-operative pain control when compared to standard of care.
  - **Null Hypothesis 1:** There will be no difference in post-operative pain control between all treatment arms.
2. **Determine the economic impact of cocktail and regional blocks in ankle fractures.** A common concern with the use of regional blocks is the cost of the additional procedure, along with logistic delays which are associated with coordinating a separate procedure. This study would provide valuable data about the additional costs associated with regional blocks and with cocktail administration which could help aid in making economically conscious treatment decisions.
  - **Hypothesis 2:** Local cocktail administration will have significantly lower costs than regional block, and not be significantly more expensive than standard of care.
  - **Null Hypothesis 2:** There is no difference in cost between the modalities.

### Secondary Aim:

**Demonstrate the use of long-acting local anesthetic as a viable pain management strategy in fracture surgery.** Although long-acting local anesthetics have an established track record in arthroplasty<sup>1-4</sup>, there is a paucity of evidence guiding their use in fractures. Small case series in trauma<sup>5</sup> and foot/ankle patients<sup>6</sup> have been encouraging, but a rigorously conducted, prospective trial in a relatively homogeneous group could generate pilot data to validate the use of long acting local anesthetics in fracture surgery. This knowledge may be translatable to other extremity injuries as well, having a greater impact than the scope of the proposed trial.

## 5. Background

Pain control after fixation of ankle fractures can improve patient satisfaction<sup>7</sup>. There has been growing interest in both multimodal pain control as well as in regional anesthesia<sup>8</sup> for improving pain control above traditional methods, which typically rely on opiates. High dose opiate use is associated with a multitude of complications, including respiratory depression, constipation, endocrine dysfunction, and complications associated with addiction/abuse<sup>9-11</sup>. Given the current focus on opiate overuse and abuse<sup>12,13</sup>, it is imperative that we decrease the use of these medications whenever possible.

For operatively treated ankle fractures, the choice of pain management is challenging. Regional anesthesia (usually in the form of a popliteal and saphenous nerve block) has been shown to be safe and have improved pain control compared to traditional treatment<sup>14</sup>, but has several drawbacks. Major concerns include the inability to monitor for nerve injury or compartment syndrome<sup>15,16</sup>, post-operative "rebound pain"<sup>17-19</sup>, the time and logistic issues involved in coordinating block placement, as well as the cost associated with an additional procedure.

Intra-operative injection of local anesthetic avoids many of the problems associated with block, but has the potential drawback of limited duration of action, as well as the theoretical issue of increasing edema and swelling in the operative area where wound healing may be a concern. There also has recently been increased interest in the use of long acting local anesthetic agents, which has been successful in joint arthroplasty<sup>1-4</sup>, but has remained limited to small case reports in the fields of trauma<sup>5</sup> and foot/ankle surgery<sup>6</sup>. Although there was initially enthusiasm for commercially prepared liposomal bupivacaine and other long-acting formulations, recent data has questioned their cost effectiveness compared to relatively inexpensive "cocktails" of multimodal pain control medications<sup>20-23</sup>.

Currently there exists little evidence to support the use of either peri-operative regional anesthetic or local anesthetic cocktail versus standard of care narcotic regimen. The primary aim of this study is to conduct a prospective, randomized control trial comparing standard pain control methods to both perioperative block and local "cocktail" anesthesia in terms of post-operative pain control, narcotic requirements, patient satisfaction, and cost. We hypothesize that local cocktail will be superior with regards to pain control when compared to both regional block and standard of care, have significantly lower overall costs, and represent the most cost-effective means of pain control in this patient population. Our null hypothesis is that there is no difference between any of the methods and the measured outcomes.

Both primary investigators have experience in the conduction of prospective trials involving patient satisfaction, outcome, and substance use. Eric Swart has prior research expertise in economic analysis and cost-effectiveness analysis, and experience in the development of multidisciplinary care pathways and protocols. Both PIs have also been involved in the direct creation of pain control protocols for the

purpose of improving patient care at their respective institutions via local, regional, and multi-modal therapies for pain control.

Both PIs are also currently the recipients of an OTA Directed Topic Grant entitled: Does the use of Liposomal Bupivacaine Decrease Narcotic Requirements in Geriatric Hip Fractures? A Randomized, Double Blinded Control Trial. This study is evaluating the effect of intra-operatively locally administered liposomal bupivacaine in geriatric hip fracture patients. Experience gained from this trial will help in successful completion of a pain control trial in ankle fractures.

General anesthesia with opiate monotherapy, regional anesthesia, and local anesthesia are all practiced as standard of care at this institution. We do not have formal data on utilization, but approximately 40% of patients get general anesthesia only, 40% of patients get regional anesthesia, and 20% get local anesthetic for post-operative pain control. In the trauma group, the local anesthesia has historically been a single agent (bupivacaine or ropivacaine), although the “cocktail” is routinely used in arthroplasty services nationwide.<sup>3,22-25</sup>

## 6. Inclusion and Exclusion Criteria

### *Inclusion Criteria*

- Age 18 – 89
- Sustained a bimalleolar ankle fracture (OTA/AO type 44 A2, B2, C1, and C2 fracture) with surgery indicated and an approach with medial and lateral incisions planned
  - Syndesmotic injuries will be included, due to the practical difficulty of reliably determining the presence of a syndesmotic injury preoperatively
  - Trimalleolar ankle fractures where fixation of the posterior malleolus is not planned will also be included
- Isolated Injury

### *Exclusion Criteria*

- Unifocal malleolar fractures
- Bimalleolar fractures where fixation of only one malleolus is planned
- Posterior malleolus fractures requiring fixation
- Patients ineligible for a peripheral nerve block (e.g. concern for compartment syndrome)
- Open injury
- Patients treated with external fixation
- Neurologic condition that would confound results (e.g. peripheral neuropathy)
- Inability to consent
- Chronic opioid use
- History of opiate abuse
- Polytrauma as defined as additional boney injury, visceral injury or moderate soft tissue injury (requiring suture repair or other invasive procedure)
- Prisoners (unlikely to be accessible for follow-up)
- Pregnant patients
- Non-English-speaking subjects (post-operative data collection procedure involves conversations via phone calls. As we do not have access to translators for this research project, we will work exclusively with English-speaking subjects).

- Subjects unable to take the standard post-operative pain regimen that consists of gabapentin, oxycodone, acetaminophen, and ibuprofen.

## 7. Study-Wide Number of Subjects

This is a multi-center study being conducted in conjunction with the University of Kentucky. The total recruitment goal is 70 patients, with a goal enrollment of 35 patients at University of Massachusetts, and 35 patients at University of Kentucky.

Recent studies looking at long acting local anesthesia arthroplasty patients or blocks in ankle fracture patients have showed a reduction in opiate use ranging from 50%-66%<sup>19,25</sup>. Within an individual patient group, variability in narcotic use has typically had standard deviations around 12.5% - 50% of the total dose<sup>18,19</sup>. Conservatively, to detect a 45% reduction in narcotics with a standard deviation of 50% of the total dose, with 80% power, 20 patients would be needed in each cohort. Allowing for a 10-20% drop-out rate gives a total of 70 patients.

## 8. Study-Wide Recruitment Methods

Recruitment methods will be the same at both University of Massachusetts and University of Kentucky. Refer to [24. Local Recruitment Methods](#) for details of recruitment methods at University of Massachusetts.

## 9. Study Timelines

- Duration of an individual subject's participation in the study

An individual subject's participation in the study begins at enrollment and ends after 12 weeks post-op follow-up period.

- Duration anticipated to enroll all subjects

From recent internal data review, we treat between 140 ankle fractures annually at UMMMC. We anticipate 30-50% of patients will be both eligible and willing to enroll in the study, so to enroll 35 patients should take 6-12 months.

- Estimated date for the investigators to complete this study (complete primary analyses)

Primary analysis should be completed once the final cohort of patients complete their 12-week study window, so we expect 13-14 months after initiation of enrollment.

## 10. Study Endpoints

- **Primary Outcome Variables:** total morphine equivalents given within 72 hours of surgery
- **Secondary Outcome Variables:** pain VAS (2, 4, 8, 12, 18, 24, 48, and 72 hours after surgery), QOR-9 score (24, 48, and 72 hours after surgery) and need for pain medication refill

## 11. Procedures Involved

- **Patient identification:** Patients will be identified on morning intake rounds by the trauma team and the research staff who are present daily to screen and enroll patients.
- **Screening/Enrollment:** The research staff will review the charts to identify patients meeting the inclusion/exclusion criteria. Patients will be approached for study participation and enrolled in the study prior to surgery. For patients seen initially in the outpatient setting, this will be done at the time of their office visit where a surgical plan is made and discussed with the patient. For patients admitted to the hospital acutely for fixation, this will be done on the inpatient floor or in the preoperative area.
  - For potential participants, the research staff will interview the patients, confirm willingness to participate and inclusion/criteria.
    - At time of enrollment, preoperative demographics will be recorded which will include age, sex, comorbidities, current use of anti-epileptic/anti-depressive medications, fracture classification (using AO/OTA classification system).
    - After this review and screening, the patient will be given the opportunity to ask researchers questions about the study. It will be reiterated to all patients during preoperative discussions that their enrollment status in no way will affect their ability to get adequate post-operative pain control.
- **Randomization:** Once enrolled, participants will undergo block randomization (block size: 9) to one of three treatments through a computer-generated algorithm. Participants will be randomized to receive patients will be randomized to receive 1) standard of care post-operative pain control with oral narcotics, 2) single injection perioperative peripheral nerve block, or 3) subcutaneous local cocktail injection at the conclusion of surgery.
- **Treatment:** Surgical approach and fixation will be performed according to the attending surgeon and is independent of the study.
  - Anesthesia: Patients in all arms will receive general anesthesia
    - Block:
      - 0.5% ropivacaine - 30mL each sciatic and femoral/saphenous nerve
      - Ultrasound guided
    - Although there is some data supporting the use of continuous nerve catheters over a single injection block<sup>18,19</sup>, we are using only a single injection nerve block as that is currently the more common procedure at our institutions and the more relevant comparison given our institutional infrastructure. Future projects could evaluate the cost and efficacy of long-acting local vs. indwelling perineural catheter based on the results of this study.
  - Cocktail mix / administration: For patients randomized to the cocktail group, the local anesthetic solution will be prepared by the pharmacy and delivered to the operating room at the conclusion of surgery and will be injected circumferentially around the incisions into the surrounding musculature, periosteum and subcutaneous layer in a standardized fashion. The cocktail mix/technique is based on published reports of solutions with demonstrated efficacy in the total joint arthroplasty literature<sup>3,23,25</sup>, although ketorolac has been removed due to theoretical concerns of the interaction between NSAIDs and fracture healing. It consists of:
    - 0.5% Ropivacaine, 24.6 mL
    - Clonidine 100 mcg/mL, 0.4mL
    - Epinephrine 1mg/mL, 0.5mL

- Saline to total volume of 50 mL (24.5mL of saline)

The total amount of solution prepared is 50mL, but typically 30mL is used based on the size of the incision. Additionally, total volume administered will be recorded.

- **Post-operative inpatient care:** While admitted to the hospital, patients will receive medical care per routine, including a standardized post-operative pain control regimen. Post-operatively, all patients will receive a uniform pain control protocol consistent with the current standard of care. We have worked with our anesthesia team to create a consensus-driven protocol to ensure patients are evaluated for pain and having pain treated in an appropriate and uniform manner. Patients will be given 30mg of Toradol IV at the end of case. All patients will receive the same post-operative pain regimen and oral regimen consisting of gabapentin, oxycodone, acetaminophen, and ibuprofen that is consistent with the standard of care. Patients will be given a detailed instruction that outlines their pain regimen: “Ankle Fx Pain Control\_H00014155\_Pain Control Handout\_06-01-18.” Protocol deviations will be recorded, and morphine equivalents will be recorded. We will collect the following data from inpatient hospitalization:
  - At the conclusion of the surgery, we will note tourniquet time, incision locations, fixation locations, and whether or not syndesmosis fixation was performed.
  - The medical record will be used to determine total morphine equivalents post-surgery, including recovery unit administration of narcotics in the immediate post-operative period.
  - It will also contain Pain Visual Analog Scale (VAS) scores administered by the nursing staff, 2 hours after surgery.
  - Prior to discharge from the hospital, patients will be given a “Pain Journal” to document their narcotic use and VAS pain scores, and asked to fill it out any time they take pain medication. Once patients are discharged from the hospital, with the aim of gathering data about the timing of “rebound pain” which has been reported after blocks and typically starts around 8-24 hours after surgery<sup>17</sup>.
  - The patients will receive phone calls at 24, 48, and 72 hours after surgery. The phone calls will be administered by the research assistant. In the cases of emergency such that the patient requires further care on an urgent basis, corresponding medical representatives (e.g. resident on call) will be reached, and the patient will be treated based on standard of care, as a part separate from the study. Total narcotic use recorded in the pain journal as well as VAS pain scores will be reviewed. We will also administer the Quality of Recovery 9 (QOR-9) questionnaire. The QOR-9 is a 9- item questionnaire that assesses the general wellbeing of post-operative patients. It has been validated in large cohorts of surgical patients<sup>26</sup>, and specifically used in studies evaluating recovery from ankle fracture surgery as well<sup>14</sup>.
- **Post-Operative Rehabilitation:** Post-operatively, patients will be immobilized in a short leg cast or splint for two weeks, until their first post-operative visit at 2-weeks where sutures will be removed. Weight bearing restrictions and DVT prophylaxis will be determined at the discretion of the treating surgeon.
- **Post-hospital follow-up:** Post-operatively, patients will be seen in clinic 2, 6, and 12 weeks after surgery. At each of these time points, wound healing and/or complications will be noted.
- **Analysis:** The primary outcome will be assessed using a non-parametric Mann-Whitney test using a Bonferroni correction for multiple comparisons. Secondary outcomes will be compared using a Wilcoxon Signed-rank test, and Chi-Square for comparison of group characteristics.
- **Economic Analysis:** In efforts to address aim 2, after the conclusion of the study, a cost analysis will be performed using the billing data. Specific cost items measured will be procedural fees associated

with blocks, cost of pain medication consumed (in all cohorts, including medications used in cocktail and in the block). We will also note length of stay (time from conclusion of surgery to discharge from hospital) as well as discharge disposition. Additional operative time due to application of local injection will not be quantified/analyzed for cost as it is a fixed-variable cost unlikely to change the global fees associated with operative fracture care. Implant costs will not be measured.

## **12. Data and Specimen Banking**

No specimens will be obtained or retained for future study. The stored deidentified data from the study will be kept for a minimum of 6 years for records in the event follow-up studies are pursued and will remain protected and encrypted. Data will be permanently deleted following this time period. The banked data will be stored on a password-protected research drive corresponding to "orthotrauma (\\umhcnas03)". Upon conclusion of the study, the data will be stored in a password encrypted file that only the PI has access to.

## **13. Data Analysis and Management**

Following initial enrollment, each patient will be assigned a unique patient identifier. All electronic documentation containing total morphine equivalents, visual analogue scores and all other medical information will be associated with this unique patient identifier during analysis. All protected health information will be stored in a separate, password-protected research file that will not be accessed regularly. Following our secondary analysis, all personal health information will be removed from our electronic files and destroyed in accordance with patient privacy guidelines.

Data obtained at UMMC during the study will be recorded and stored using excel spreadsheet that will be maintained at the hospital by the research staff. The University of Kentucky will be responsible for their own data infrastructure. Upon conclusion of the study, the University of Kentucky will share de-identified data (with information relating to the study endpoints) with the University of Massachusetts for final analysis. Final analysis will be conducted using Excel spreadsheets. All documents will be stored on a password-protected research drive and only research personnel will have access to its content. Paper documents, including consent forms, will be stored in a locked cabinet in a secure research room.

Each researcher on the project has passed the CITI exam on ethical conduct of research and has received training and supervision regarding patient confidentiality. Only approved research personnel will administer consents and perform phone surveys. All efforts will be made to maintain the confidentiality of the patient reported data. Only study personnel listed in eIRB will have access to identified study data.

Consistent with other research projects through the UMass Orthopedic Trauma Center, all other research-related files including but not limited to copies of consents and surveys will be stored on a password protected research drive or locked research cabinet. Research personnel also have allocated space with locked drawers for source document files and secure workspace apart from patient or public areas that is also locked.

## **14. Provisions to Monitor the Data to Ensure the Safety of Subjects**

Subjects in this study will be exposed to minimal risk as all three treatment arms are considered standard postsurgical care. The patients are monitored continuously as inpatients post-operatively and any issues



with medication effects, wound healing, or other medical complications will be logged as adverse events. Blinding will only be broken for unexpected complications. The research team will meet monthly to monitor data collection and handling. During this time, study staff will also review adverse events logs and pain scores.

## **15. Withdrawal of Subjects Without Their Consent**

We do not anticipate any situation in which a subject would be withdrawn from the study by the researchers should they wish to remain. We anticipate analyzing the data via an intention to treat analysis and thus would include data from all subjects initially enrolled, even if they developed an intolerance or medical contraindication to continuing the study.

However, a subject may choose to withdraw from the study on their own accord, at any time, for any reason. Contact information and instructions detailing how to withdraw from the study will be provided in the consent form and will involve contacting the principal investigator directly. If a subject chooses to withdraw, any and all data that was previously collected will be included in the analysis; however, we will cease any further data collection. All personal health information collected prior to a patient's withdrawal from the study will be destroyed in accordance with patient privacy laws. In addition, any paper documents obtained will be destroyed in accordance with standard HIPPA guidelines. Upon being notified of a patient's decision to withdraw from the study, researchers will no longer contact the patient via phone, administer surveys, or access their medical information online.

## **16. Risks to Subjects**

Surgical risks are described to the patient prior to surgery and are part of standard of care procedures for ankle fracture surgery. There are no additional surgical risks to patients who participate in this study.

The medications used post-operatively are commonly used for treatment of pain following surgery and carry the same risks when taking these medications for postoperative care. These represent the standard of care for post-operative pain control, and are already part of our existing post-operative pain control pathway.

The treatment arms of this study involve randomization to general anesthesia (no additional pain control), regional anesthesia, or long acting local anesthesia cocktail. Regional blocks are routinely performed at this institution, and has the following risks: short-term pain at the site of block administration, bleeding, infection, or nerve injury. Local anesthesia administration is also routinely performed, and has the potential risk of additional wound complications.

Although the medications given in both regional blocks and local anesthesia have cardiovascular and risk profiles, those risks are generally for systemic administration. When given locally, the systemic medical effects are effectively minimized. Our regional anesthesia team does not currently have any medical contraindications to performing nerve blocks (including renal or hepatic disease). Likewise, there are no standard medical contraindications to delivering local anesthetics to the surgical site. Nevertheless, the risks listed on the FDA insert of each of the individual components of the nerve block medication and long-acting local anesthesia cocktail are listed in the consent form.

There is also a risk of a breach of confidentiality. All research team members are appropriately trained and understand the importance of confidentiality.

## **17. Potential Benefits to Subjects**

The addition of local or regional anesthesia could potentially benefit patients by resulting in improved pain control, reduced opiate requirements, and a resultant decrease in medical complications.

## **18. Vulnerable Populations**

Patients unable to consent for themselves will be excluded. Whenever possible, we will also discuss involvement in the study with the patient's family (provided the patient gives permission for us to discuss with them) to ensure that the decision to participate in the study is made with appropriate consideration and that the entire family is comfortable with involvement.

## **19. Multi-Site Research**

This study is being conducted in conjunction with the University of Kentucky. Both have equivalent recruitment goals. The two principal investigators, Eric Swart and Paul E. Matuszewski, are close colleagues who remain in constant communication and will maintain coordination to ensure that:

- All sites have the most current version of the protocol, consent document, and HIPAA authorization.
- All required approvals are obtained at each site (including approval by the site's IRB of record).
- All modifications are communicated to sites and approved (including approval by the site's IRB of record) before the modification is implemented.
- All engaged participating sites safeguard data as required by local information security policies.
- All local site investigators conduct the study appropriately.
- All non-compliance with the study protocol or applicable requirements is reported in accordance with local policy.
- All sites are informed of problems, interim results, and the study closure.

## **20. Community-Based Participatory Research**

N/A

## **21. Sharing of Research Results with Subjects**

At the conclusion of the study, following de-identification and data analysis, results of this data collection may be shared with patients who have participated in this research as it becomes available, if they request it verbally or in writing. This will only occur after final data analysis, if a subject inquires.

## **22. Setting**

Research subjects will be identified, recruited and followed post-operatively as inpatients at the University Campus of UMass Memorial Medical Center (UMMMC). They will be followed post-discharge at the

Ambulatory Care Center (ACC). Data analysis will primarily occur in locked, private offices at in one of two secure research offices located at the University Campus.

## **23. Resources Available**

UMass Memorial is the largest health system in central Massachusetts. It consists of three separate campuses, Hahnemann, Memorial, and University campus. The Orthopedics Department has locations on all three campuses that each provide a dedicated research space, which contain computers with access to password-protected research drives.

The Principle Investigator (PI) and the Co-Investigator will be responsible for overseeing the study and ensuring consistency throughout the project. The principal investigator will serve as the research coordinator and assist in data collection and analysis. The co-investigator of the project will serve as the representative of the anesthesiology team and be responsible for coordination between the anesthesiology team and the research team. Recruitment and consent will be performed by the PI or the research assistant. Each member of the research staff has passed the CITI exam on ethical conduct of research and have received training and supervision regarding patient confidentiality and study protocol. The PI will meet with all research staff periodically to review each role and ensure adequate training for the respective positions. Upon enrollment of each patient, the corresponding surgical team will be counseled concerning the details of the study and their role, prior to admitting the patient into the OR.

The hospital research pharmacy has been approached about this study and a protocol is in place to ensure treatment occurs for the study-related portion.

The PI and research assistant will be responsible for institutional /IRB communication as well as data review and assistance with follow-up patient coordination as needed. There are no anticipated adverse consequences associated with this study, however, the principal investigator and the research assistant will both be available should any unexpected medical or psychological problems arise. The research subjects will be provided with appropriate contact information in the consent form and will be provided with the PIs contact information at the time of enrollment as well.

## **24. Local Recruitment Methods**

No formal external recruitment methods will be used for this study, as ankle fracture patients are universally admitted to the hospital after injury while awaiting surgery. Patients will be identified, screened, and approached for enrollment in the study as noted above (see [9. Study Timeline](#)). After review and screening, the patient will be given the opportunity to ask researchers questions about the study. It will be reiterated to all patients during preoperative discussions that their enrollment status in no way will affect their ability to get adequate post-operative pain control. There will be no financial compensation in return for participation in this study.

## **25. Local Number of Subjects**

The local recruitment goal at University of Massachusetts is 35 patients (see [7. Study-Wide Number of Subjects](#))

## **26. Confidentiality**

As part of our design, all patient will be assigned a unique patient identifier. All patient personal information will be stored in a data collection excel file, only linked with that patient identifier. A master list that links the patient's identifier to their medical record number and name will be maintained in a separate, locked file that only approved research personnel will have access to. During the data collection period, researchers will not directly use this master list and, instead, will draw upon information from a separate that contains only the patient's unique patient identifier.

All paper data collection documents are kept in locked file cabinets within locked offices that are accessible only to the project investigators and staff. All online databases are password protected to guard against unauthorized access and only approved research personnel will be granted access.

## **27. Provisions to Protect the Privacy Interests of Subjects (HIPAA)**

All eligible subjects will identified by orthopedic trauma team and researchers during morning intake rounds. After this point, only approved research personnel will have access to patients' private health information. All research will be stored electronically on secure research drives or locked offices as described above.

Only health information related to their orthopedic injury and surgery will be reviewed for the purposes of this study. Other unrelated personal health information will not be accessed or used in any way. All subjects will sign a HIPAA authorization form for use of any protected health information to be used for research purposes, as stated above.

## **28. Compensation for Research-Related Injury**

There will be no additional compensation for research related injury as all treatments/medications are approved for postoperative pain management. Patients would be treated for any complications of surgery including non-union or fractures that may be slow to heal using approved methods by their treating surgeon consistent with standard of care. The patient would be responsible for all costs associated with this treatment.

## **29. Economic Burden to Subjects**

All treatment costs are within the standard of care and the expenses will be paid for by the patient and their health insurance. There is no additional post-operative follow-up required for this study beyond the surgeon's standard follow-up routine. There will be no financial compensation in return for participation in this study.

## **30. Consent Process**

We will obtain consent in accordance with the guidelines from the HRP-802 INVESTIGATOR GUIDANCE: Informed Consent (<http://www.umassmed.edu/ccts/irb/investigator-guidance/>). The consenting process will take place in the University Campus of UMass Memorial Medical Center (UMMMC) as previously described. All research personnel administering consents will be provided with copies of the above inclusion and exclusion criteria to apply to potential study participants. All subjects have the option to

withdraw from the study at any time point by contacting the principal investigator. Consent will only be obtained by approved research personnel who have passed the CITI exam for ethical conduct of research.

Patients will be given ample time to review the contents of the consent in private. The patient will be approached about the study as soon as they are identified to give them adequate time to review the study information prior to surgery. A researcher will then be available to answer all questions regarding the patient's participation in the study, including but not limited to all risks and benefits. The patient may refuse to participate at any time during the consenting process or over the course of the study.

### 31. Process to Document Consent in Writing

The consent will be documented in accordance with the guidelines detailed previously in the HRP-803 INVESTIGATOR GUIDANCE: Documentation of Informed Consent. The patient will receive a copy of this consent for their personal records during the enrollment process. This consent has been largely modeled after the Template Consent Document (HRP-502) and provides answers to many anticipated questions. Each signed consent will be stored in a locked cabinet in a secure research office that only approved study personnel are able to access.

### 32. Drugs or Devices

For information on drugs, please refer to the Treatment section in 11. Procedures Involved. Devices used for fixation of the ankle fracture are determined by the attending surgeon based on the injury characteristics, and are independent of involvement in this study.

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